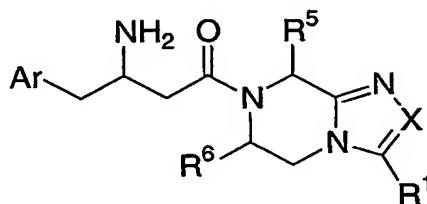


WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

Ar is phenyl which is unsubstituted or substituted with 1-5 of R³, wherein R³ is independently selected from the group consisting of:

- (1) halogen,
- (2) C₁₋₆ alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,
- (3) C₁₋₆ alkoxy, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,
- (4) CN, and
- (5) hydroxy;

X is selected from the group consisting of:

- (1) N and
- (2) CR²;

R¹ and R² are each independently selected from the group consisting of:

- (1) hydrogen,
- (2) CN,
- (3) C₁₋₁₀ alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 halogens or phenyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NHSO₂R⁴, SO₂R⁴, CO₂H, and CO₂C₁₋₆ alkyl, wherein the CO₂C₁₋₆ alkyl is linear or branched,
- (4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NHSO₂R⁴,

SO₂R⁴, CO₂H, and CO₂C₁₋₆alkyl, wherein the CO₂C₁₋₆alkyl is linear or branched, and

- (5) a 5- or 6-membered heterocycle which may be saturated or unsaturated comprising 1-4 heteroatoms independently selected from N, S and O, the heterocycle being unsubstituted or substituted with 1-3 substituents independently selected from oxo, OH, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens;
- 10 R⁴ is C₁₋₆ alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 groups independently selected from halogen, CO₂H, and CO₂C₁₋₆ alkyl, wherein the CO₂C₁₋₆ alkyl is linear or branched;
- R⁵ and R⁶ are each independently selected from the group consisting of:
- 15 (1) hydrogen,
- (2) C₁₋₁₀ alkyl, which is linear or branched and which is unsubstituted or substituted with one or more substituents selected from:
- (a) halogen,
- (b) hydroxy,
- 20 (c) phenyl, wherein the phenyl is optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens,
- 25 (d) naphthyl, wherein the naphthyl is optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens,
- 30 (e) CO₂H,
- (f) CO₂C₁₋₆ alkyl,
- (g) CONR⁷R⁸, wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen, tetrazolyl, phenyl,

C₃₋₆ cycloalkyl and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is linear or branched and is optionally substituted with 1-6 substituents independently selected from 0-5 halogen and 0-1 phenyl, wherein the phenyl or C₃₋₆ cycloalkyl being R⁷ or R⁸ or the optional phenyl substituent on the C₁₋₆ alkyl are optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy, said C₁₋₆ alkyl and C₁₋₆ alkoxy being linear or branched and optionally substituted with 1-5 halogens, or wherein R⁷ and R⁸ are optionally joined to form a ring selected from pyrrolidine, piperidine or morpholine,

(3) CN,

(4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy and halogen, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens,

(5) naphthyl which is unsubstituted or substituted with 1-5 substituents independently selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy and halogen, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens,

(6) CO₂H,

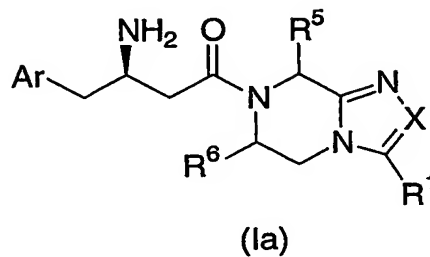
(7) CO₂C₁₋₆ alkyl,

(8) CONR⁷R⁸, and

(9) C₃₋₆ cycloalkyl, which is optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens,

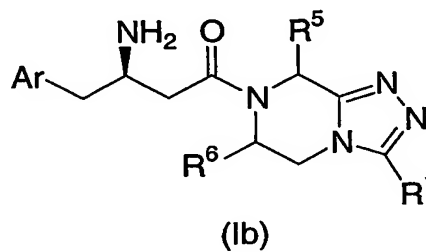
with the proviso that one of R⁵ and R⁶ is other than hydrogen; or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 of the formula Ia:



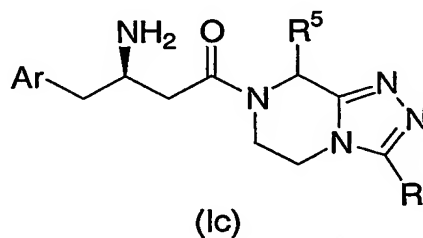
or a pharmaceutically acceptable salt thereof.

- 5 3. The compound of Claim 2 of the formula Ib:



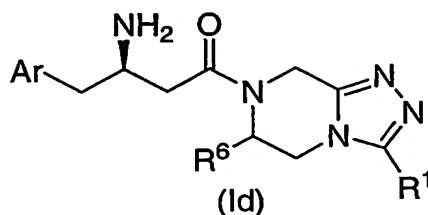
or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 3 of the formula Ic:



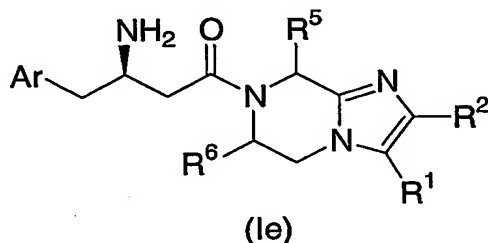
or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 3 of the formula Id



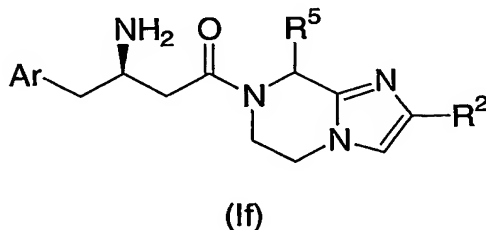
or a pharmaceutically acceptable salt thereof.

- 5 6. The compound of Claim 2 of the formula Ie:



or a pharmaceutically acceptable salt thereof .

7. The compound of Claim 6 of the formula If:



10

or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 1 wherein Ar is phenyl which is unsubstituted or substituted with 1-5 substituents which are independently selected from the group consisting of:

15

- (1) fluoro,
- (2) chloro, and
- (3) CF₃.

9. The compound of Claim 8 wherein Ar is selected from the group consisting of:

- (1) phenyl,
- (2) 2-fluorophenyl,
- (3) 3,4-difluorophenyl,
- (4) 2,5-difluorophenyl,
- (5) 2,4,5-trifluorophenyl, and
- (6) 2-fluoro-4-(trifluoromethyl)phenyl.

10. The compound of Claim 1 wherein R¹ is selected from the group consisting of:

- (1) hydrogen and
- (2) C₁₋₆ alkyl, which is linear or branched and which is unsubstituted or substituted with phenyl or 1-5 fluorines.

11. The compound of Claim 10 wherein R¹ is selected from the group consisting of:

- (1) hydrogen,
- (2) methyl,
- (3) ethyl,
- (4) CF₃,
- (5) CH₂CF₃,
- (6) CF₂CF₃, and
- (7) benzyl.

12. The compound of Claim 11 wherein R¹ is selected from the group consisting of:

- (1) hydrogen,
- (2) methyl,
- (3) ethyl,
- (4) CF₃, and
- (5) CH₂CF₃.

13. The compound of Claim 12 wherein R¹ is hydrogen or CF₃.
14. The compound of Claim 1 wherein R² is selected from:
- 5 (1) hydrogen,
(2) C₁₋₆alkyl, which is linear or branched and which is
unsubstituted or substituted with 1-5 fluorines, and
(3) phenyl, which is unsubstituted or substituted with 1-3
substituents independently selected from fluoro, OCH₃, and
OCF₃.
- 10 15. The compound of Claim 14 wherein R² is selected from the
group consisting of:
- 15 (1) hydrogen,
(2) methyl,
(3) ethyl,
(4) CF₃,
(5) CH₂CF₃,
(6) CF₂CF₃,
(7) phenyl,
20 (8) (4-methoxy)phenyl,
(9) (4-trifluoromethoxy)phenyl,
(10) 4-fluorophenyl, and
(11) 3,4-difluorophenyl.
- 25 16. The compound of Claim 15 wherein R² is CF₃ or CF₂F₃.
17. The compound of Claim 1 wherein R⁵ and R⁶ are
independently selected from the group consisting of:
- 30 (1) hydrogen,
(2) C₁₋₁₀ alkyl, which is linear or branched and which is unsubstituted or
substituted with one or more substituents selected from:
- (a) halogen,
(b) phenyl, wherein the phenyl is optionally substituted with 1-5
substituents independently selected from halogen, OH,

C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens, and

(3) phenyl which is unsubstituted or substituted with 1-3 substituents independently selected from C₁₋₆alkyl, OC₁₋₆alkyl, and halogen, wherein the C₁₋₆alkyl and OC₁₋₆alkyl are linear or branched and optionally substituted with 1-5 halogens, and

(4) CO₂C₁₋₆ alkyl,

with the proviso that one of R⁵ and R⁶ is other than hydrogen.

18. The compound of Claim 17 wherein R⁵ and R⁶ are independently selected from the group consisting of:

(1) hydrogen,

(2) CH₃,

(3) CH₂CH₃,

(4) CH(CH₃)₂,

(5) COOCH₃,

(6) CH₂-phenyl,

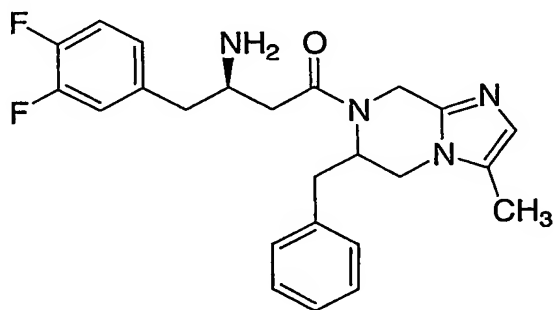
(7) 3-fluorophenyl, and

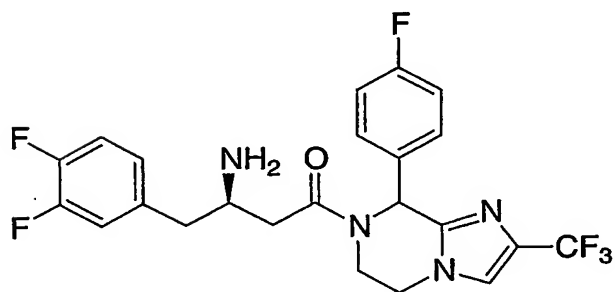
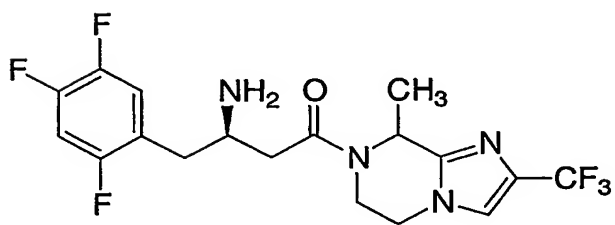
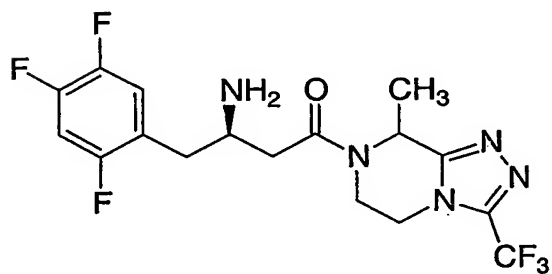
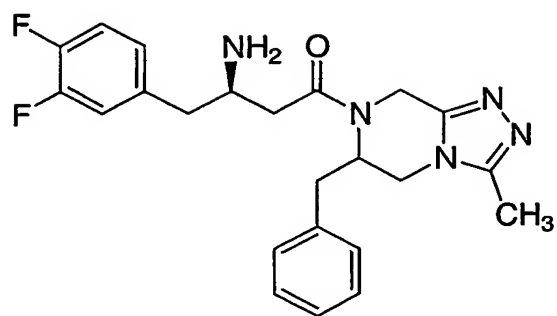
(8) 2-(trifluoromethyl)phenyl,

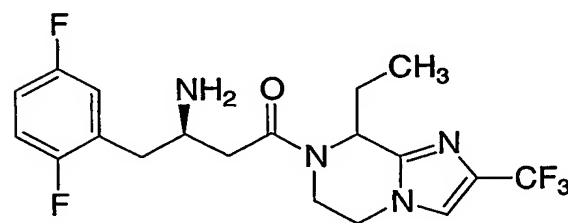
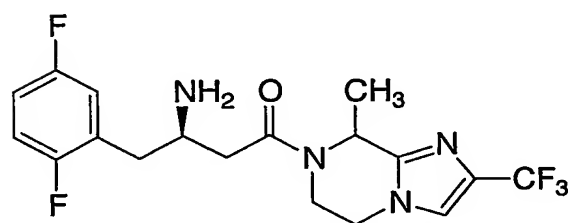
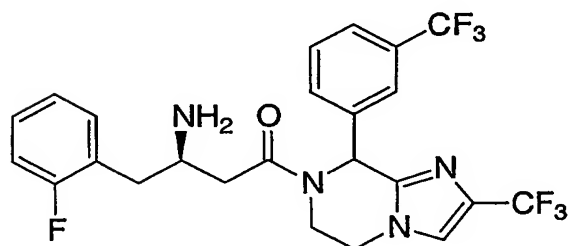
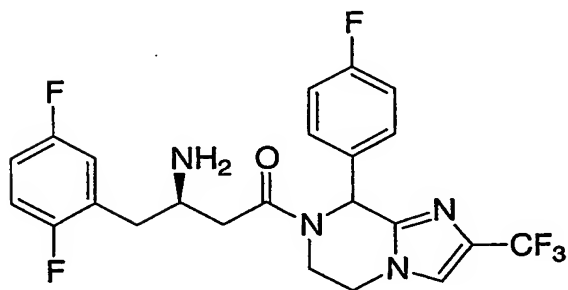
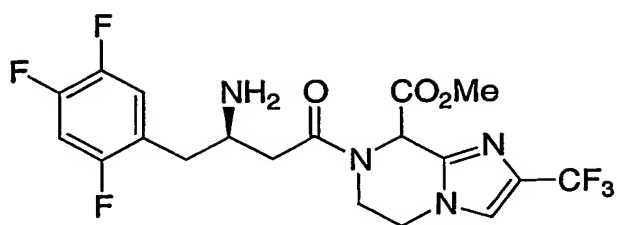
with the proviso that one of R⁵ and R⁶ is other than hydrogen.

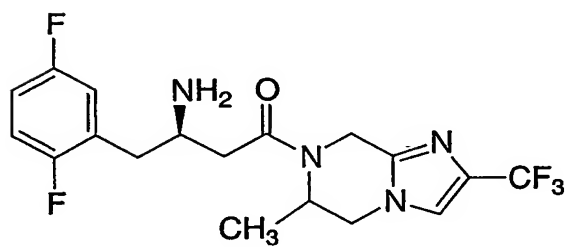
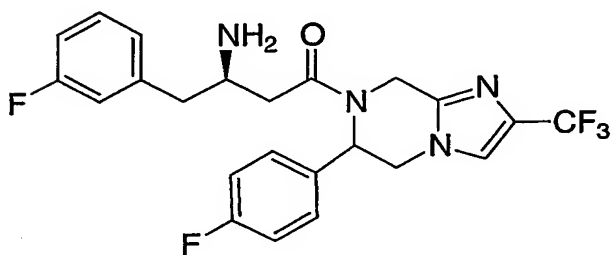
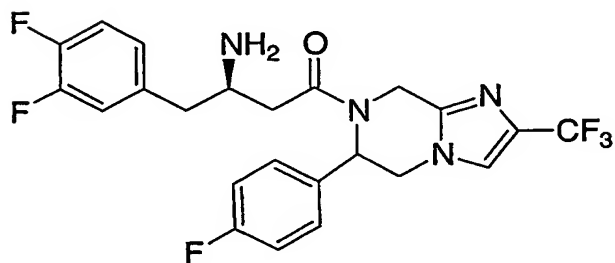
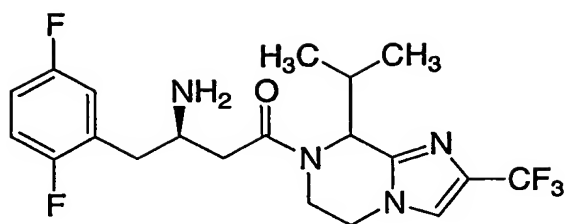
19. The compound of Claim 18 wherein R⁵ and R⁶ are independently hydrogen or CH₃, with the proviso that one of R⁵ and R⁶ is other than hydrogen.

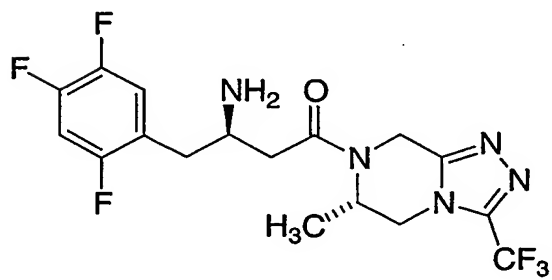
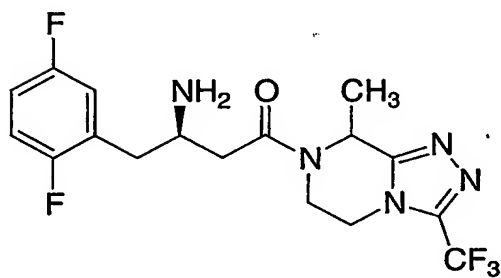
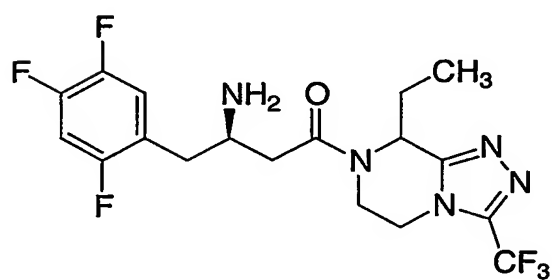
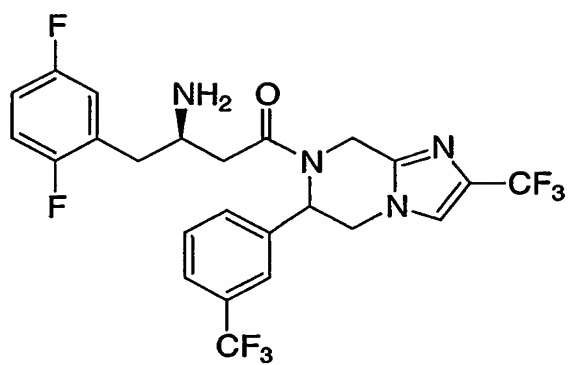
20. A compound which is selected from the group consisting of:

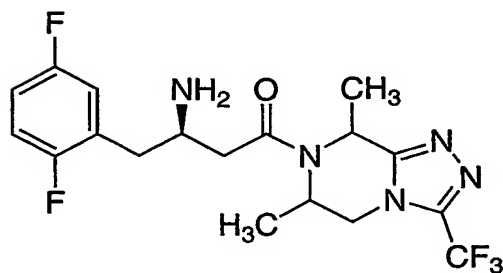
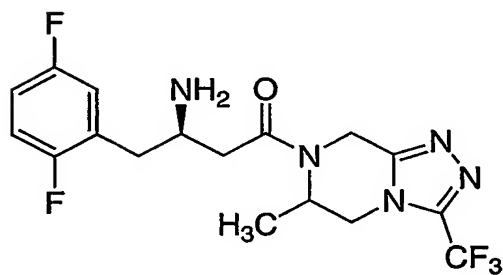
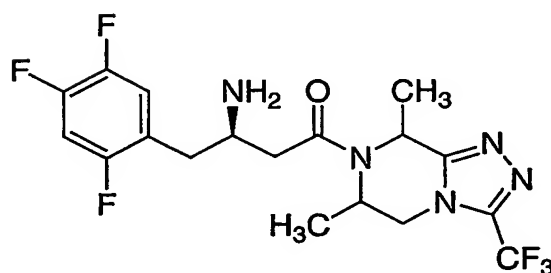
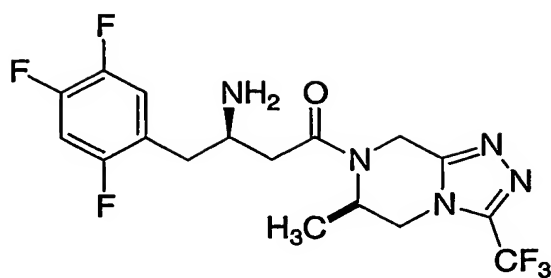












5 or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

22. A method for inhibition of dipeptidyl peptidase-IV enzyme activity in a mammal which comprises the administration to a mammalian patient in need thereof an effective amount of a compound of Claim 1.

5 23. A method for treating, controlling, ameliorating or reducing the risk of diabetes comprising the administration to a mammalian patient in need thereof a therapeutically effective amount of a compound of Claim 1.

10 24. A method for treating, controlling, ameliorating or reducing the risk of non-insulin dependent (Type 2) diabetes mellitus in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

15 25. A method for treating, controlling, ameliorating or reducing the risk of hyperglycemia in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

20 26. A method for treating, controlling, ameliorating or reducing the risk of obesity in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

25 27. A method for treating, controlling, ameliorating or reducing the risk of insulin resistance in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

30 28. A method for treating, controlling, ameliorating or reducing the risk of one or more lipid disorders selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

29. A method for treating, controlling or preventing atherosclerosis in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

5 30. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) hypertension and other disorders where insulin resistance is a component, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

31. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type 2 diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, and other conditions that may be affected by inhibition of DP-IV, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a first compound of Claim 1, or a pharmaceutically acceptable salt thereof, and one or more other compounds selected from the group consisting of:

- (a) other dipeptidyl peptidase IV (DP-IV) inhibitors,
- (b) insulin sensitizers selected from the group consisting of (i) PPAR γ agonists, other PPAR ligands, PPAR α/γ dual agonists, and PPAR α agonists, (ii) biguanides, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;
- 5 (c) insulin or insulin mimetics;
- (d) sulfonylureas or other insulin secretagogues;
- (e) α -glucosidase inhibitors;
- (f) glucagon receptor agonists;
- (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;
- 10 (h) GIP, GIP mimetics, and GIP receptor agonists;
- (i) PACAP, PACAP mimetics, and PACAP receptor agonists;
- (j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinic alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists, (v) PPAR α/γ dual agonists, (vi) inhibitors
- 15 of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, and (viii) anti-oxidants;
- (k) PPAR δ agonists;
- (l) antiobesity compounds;
- (m) ileal bile acid transporter inhibitors;
- 20 (n) antihypertensives; and
- (o) anti-inflammatory agents.

32. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of

25 hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, which method comprises administering to a mammalian patient in need thereof a therapeutically effective amount of a compound of Claim 1 and an HMG-CoA reductase inhibitor.

30 33. The method of Claim 32 wherein the HMG-CoA reductase inhibitor is a statin.

34. The method of Claim 33 wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin,

35 rivastatin, itavastatin, and rosuvastatin.

35. A method for treating, controlling, ameliorating or reducing the risk of atherosclerosis in a mammalian patient in need thereof comprising the administration to the patient of an effective amount of a compound of Claim 1 and an effective amount of an HMG-CoA reductase inhibitor.

36. The method of Claim 35 wherein the HMG-CoA reductase inhibitor is a statin.

37. The method of Claim 36 wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, and rosuvastatin.

38. A pharmaceutical composition for treating, controlling, ameliorating or reducing the risk of atherosclerosis, comprising: (1) a compound of Claim 1, (2) an HMG-CoA reductase inhibitor, and (3) a pharmaceutically acceptable carrier.

39. A method of treating diabetes in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with the PPAR α / γ dual agonist KRP-297.

40. The pharmaceutical composition of Claim 21 further comprising one or more additional active ingredients selected from the group consisting of:

- (a) a second dipeptidyl peptidase IV inhibitor;
- (b) an insulin sensitizer selected from the group consisting of a PPAR γ agonist, a PPAR α / γ dual agonist, a PPAR α agonist, a biguanide, and a protein tyrosine phosphatase-1B inhibitor;
- (c) an insulin or insulin mimetic;
- (d) a sulfonylurea or other insulin secretagogue;
- (e) an α -glucosidase inhibitor;
- (f) a glucagon receptor antagonist;
- (g) GLP-1, a GLP-1 mimetic, or a GLP-1 receptor agonist;
- (h) GIP, a GIP mimetic, or a GIP receptor agonist;

- (i) PACAP, a PACAP mimetic, or a PACAP receptor agonist;
(j) a cholesterol lowering agent such as (i) HMG-CoA reductase inhibitor, (ii) sequestrant, (iii) nicotiny alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonist, (v) PPAR α / γ dual agonist, (vi) inhibitor of cholesterol absorption,
5 (vii) acyl CoA:cholesterol acyltransferase inhibitor, and (viii) anti-oxidant;
(k) a PPAR δ agonist;
(l) an antiobesity compound;
(m) an ileal bile acid transporter inhibitor;
(n) an anti-inflammatory agent; and
10 (o) an antihypertensive agent.

41. The pharmaceutical composition of Claim 40 wherein the PPAR α / γ dual agonist is KRP-297.